DYRUPEG

RISK MANAGEMENT PLAN (RMP)

Risk Management Plan for DYRUPEG

RMP version to be assessed as part of this application:

RMP Version number	0.3
Data lock point for this RMP	27-Jun-2024
Date of final sign off	10-Dec-2024
Rationale for submitting an updated RMP	RMP has been updated as per the comment received from EMA.
Summary of significant changes in this RMP	Part VI "Summary of the Risk Management Plan" has been updated to be inline with the updates carried out in other parts of RMP. This is to align with D180 response.

Others RMP versions under evaluation:

RMP Version Number	NA
Submitted on	NA
Procedure number	NA

Details of the currently approved RMP:

Version Number	NA
Approved with procedure	NA
Date of approval (opinion date)	NA

QPPV Name	Dr. Martina Liskova
QPPV Signature with Date	[redacted] Date: 10.12.2024
Contact person for this RMP	[redacted]
E-mail address or telephone number of contact person	[redacted]

List of abbreviations

ADA/Nab: Anti-drug antibody/ Neutralizing antibody

ALT: Alanine aminotransferase

ALP: Alkaline phosphatase

ADR: Adverse Drug Reaction

ANC: Absolute Neutrophil count

AST: Aminotransaminase

ATC: Anatomical Therapeutic Chemical

AUC: Area Under the Curve

AUECt : The area under the whole blood activity versus time effect curve was calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration

AUCi: Area under the serum concentration versus time curve from time zero to infinity

AUCt: Area under the serum concentration versus time curve from the zero time point to the last quantifiable concentration

AML: Acute Myeloid Leukaemia

ARDS: acute respiratory distress syndrome

BMI: body mass index

CI: Confidence Interval

CLS: Capillary leak syndrome

Cmax: Maximum measured serum concentration

CV: Curriculum Vitae

EEA: European Economic Area

ECG: Electrocardiogram

EPAR: European Public Assessment Report

G-CSF: Granulocyte Colony-Stimulating Factor

ICSR: Individual Case Safety Report

IV: Intravenous

ICH: International Council for Harmonisation. of. Technical Requirements. for Pharmaceuticals for Human Use

ICF: informed consent form

IMP: Investigational Medicinal Product

Kel: Elimination Rate Constant

LFTs: Liver Function Tests

LSM: Least-squares means

MAH: Marketing Authorization Holder

MDS: Myelodysplastic syndrome

NHL: Non-Hodgkin's Lymphoma

PEG: polyethylene glycol

PIL: Product Information Leaflet

PK: Pharmacokinetics

PSUR: Periodic Safety Update Report

QPPV: Qualified Person for Pharmacovigilance

RMP: Risk Management Plan

SmPc: Summary of Product Characteristics

SC: Subcutaneous

SCT: Sickle Cell Trait

Tmax: Time of the maximum measured serum concentration

UK: United Kingdom

Table of Contents

Part I: Product(s) Overview

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Pegfilgrastism
Pharmacotherapeutic group(s) **(ATC Code)**	Immunostimulants, Colony stimulating factors; (L03AA13)
Marketing Authorisation Holder	CuraTeQ Biologics s.r.o. Trtinova 260/1, Prague, 19600, Czech Republic
Medicinal products to which this RMP refers	01
Invented name(s) in the European Economic Area (EEA)	Dyrupeg 6mg/0.6mL solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralised Procedure (H0006407)
Brief description of the product Chemical class	Pegfilgrastim is a biosimilar medicinal product. It is chemically described as (2R, 4S, 5R, 6R) – 2 - [[(2R,3R,4R,5R,6S)-5-acetamido-6-[(1S,2R)-1-amino-1-carboxypropan-2-yl]oxy -3, 4 - dihydroxyoxan-2-yl]methoxy]-4-hydroxy-5-[[2-(2-methoxyethoxycarbonylamino)acetyl]amino]-6-[(1R,2R)-1,2,3-trihydroxypropyl]oxane-2-carboxylic acid. Molecular formula of Pegfilgrastim is $C_{27}H_{46}N_4O_{19}$ with a Molecular weight of 730.674 g/mol; 39 kDa1.
Summary of mode of action:	Pegfilgrastim is a PEGylated form of rhGCSF that acts on hematopoietic cells by binding to GCSF receptor, increases the proliferation and differentiation of neutrophils from committed progenitor cells, induces maturation, and enhances

	the survival and function of mature neutrophils, resulting in dose-dependent increase in neutrophils.
Important information about its composition	Origin of active substance: E. coli (harbouring the transgene encoding rhGCSF are grown in bioreactors, in growth medium and using culture conditions optimized for product yield and quality).
Hyperlink to the Product Information	Dyrupeg 6mg/0.6mL solution for injection in pre-filled syringe **(SmPC, PIL and Labelling)**
Indication(s) Current	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and Myelodysplastic syndromes).
Dosage Current	Posology One 6mg/0.6mL dose (a single pre-filled syringe) of Pegfilgrastism is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.
Pharmaceutical form(s) and strengths Current	Solution for injection in pre-filled syringe, 6mg/0.6mL
Is/will the product be subject to additional monitoring?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

In view of the EMA Guideline, no animal studies have been performed with Dyrupeg and the results of Neulasta® are described in this section[1]

Toxicity

Single and repeat dose toxicity: A full set of conventional toxicity tests were performed for pegfilgrastim. Single and repeat dose toxicity tests were conducted in rats and monkeys.

Key issues identified from acute or Repeat-dose toxicity studies

In a single dose toxicity study, pegfilgrastim was generally well-tolerated and caused expected pharmacological effects when given as IV bolus doses of 100-10,000 μg/kg to male and female rats. No mortalities occurred in the two weeks following treatment.

In repeat-dose toxicity studies in rats (weekly dosing for up to 6 months) and cynomolgus monkeys (weekly dosing for 4 weeks) pegfilgrastim produced a range of changes that reflected an exaggerated pharmacological response, or a reaction to the primary response (myeloid hyperplasia in bone marrow), such as extramedullary haematopoiesis in the spleen and liver. Animal:human systemic exposure ratios in terms of relative AUCs were up to 7.5 at 6 months in the rat and 3.5 in the monkey at 3 weeks. All of the treatment-related changes were reversible in both species.

Reproductive /developmental toxicity

The programme of reproductive toxicity tests using SC administration included a joint male/female fertility test and conventional segment II/III tests for embryo-foetal development and peri-/post-natal development.

Reproductive toxicity studies on pegfilgrastim indicated that the drug is unlikely to impair male or female fertility, not expected to be teratogenic or to affect pup development. In the rat embryo-foetal study, the only minor treatment-related foetal abnormality was wavy ribs. Placental transfer of pegfilgrastim in the pregnant rat was extremely low, systemic exposure of the foetus being < 0.5% of that in the mother. The pregnant rabbit exhibited marked reductions in maternal growth rate and a high incidence of abortions and resorptions at higher doses. The high susceptibility of the rabbit in terms of foetal loss relative to that in man is unknown and so use of pegfilgrastim in pregnancy should be discouraged.

Reproductive toxicity studies were performed in the rat and rabbit with Pegfilgrastim. The studies with pegfilgrastim indicated that the drug is unlikely to impair male or female fertility, is not

expected to be teratogenic or to affect pup development. Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every other day at doses as low as 50 µg/kg. Nonclinical data in pregnant rats indicate that very low levels of pegfilgrastim may cross the placenta. Pegfilgrastim administered SC to pregnant rabbits at doses of 200 and 250 µg/kg every-other-day during the period of organogenesis was associated with an increased incidence of abortions

Genotoxicity

Given the chemical structure and bioreactivity of pegfilgrastim it was considered inappropriate to undertake genetic toxicity studies, which is consistent with ICH Guidelines on products of biotechnological origin.

Carcinogenicity

No experimental evaluation of carcinogenic potential has been undertaken and was appropriately justified. Pegfilgrastim is most unlikely to be carcinogenic in view of:

- The limited distribution of cells with appropriate receptors
- Its cell type-specific mitogenic effects
- Its limited duration of therapy
- Data from transgenic models of overexpression of G-CSF
- Clinical experience with pegfilgrastim.

Safety pharmacology

Specific tests on acute effects on vital organ functions were not performed.

Drug Interactions

Pegfilgrastim undergoes receptor mediated endocytosis, and is unlikely to be a candidate for drug - drug interactions. Therefore, no *in vitro* interaction studies or specific *in vivo* clinical drug interaction studies have been performed.

Other toxicity – related information or data

No other toxicity studies were performed.

Part II: Module SIII - Clinical trial exposure

Two Phase I studies have been completed for this product. The study details are as follow.

A total of 308 subjects were enrolled in randomized, single-dose, double-blind, two-sequence, two-period crossover studies to compare the Pharmacokinetics, Pharmacodynamic, Immunogenicity and Safety of BP14 (pegfilgrastim) with EU-approved Neulasta® in Healthy Male Adult Subjects.

Table 2: Clinical studies with BP14 (pegfilgrastim)

Study Protocol	Study Title	Total Objective enrolment to-date
BP14-101	Comparison of BP14 (pegfilgrastim) with EU-approved Neulasta® in Healthy Male Adult Subjects	Of the total 124 healthy male adult subjects, 55 subjects had completed the study in sequence AB, and 58 in sequence BA.
C1B02880	Comparison of BP14 (pegfilgrastim) with 'Neulasta' (Pegfilgrastim) in Healthy Male Adult Subjects	Of the total 184 healthy male adult subjects, 88 subjects had completed the study in sequence AB, and 87 in sequence BA.

Immunogenicity Assessment conclusion: The overall incidences of ADA assessment were found comparable between test product BP14 and reference product Neulasta.

NAB Assessment conclusion: The overall Nab assessment was found comparable between test product BP14 and reference product Neulasta

Safety Results

The safety profiles of the BP14 (Peg filgrastim) treatment group, and Neulasta treatment group were similar with no relevant trends or clinically significant findings. Treatment-emergent AEs reported during the study were similar across treatment group BP14 (Pegfilgrastim) treated subjects and Neulasta group treated subjects.

Overall Conclusions

BP14 (Pegfilgrastim) and Neulasta are concluded to have no clinically meaningful differences in PK parameters, following the subcutaneous administration of a single 6 mg/0.6 ml dose in healthy adult male subjects in two crossover study.

The BP14 and Neulasta are concluded to have no clinically meaningful differences in pharmacodynamic parameters established PD similarity (Bioequivalence). Treatment with BP14 6 mg/0.6ml as a subcutaneous administration was safe and well-tolerated in healthy adult male subjects in this study. The safety and tolerability were comparable to the approved Reference product Neulasta.

Table SIII.1: Duration of exposure

Subject exposure to IMP (Dyrupeg or Neulasta®) is summarized below:

Table 3: Exposure of Subjects to Investigational Products in the studies BP14-101 and C1B02880

Dyrupeg		**Neulasta®**	
Treatment Period 1	154	Treatment Period 1	154
Treatment Period 2	145	Treatment Period 2	143
Total	**299**		**297**

A total of 20 subjects discontinued treatment during the studies

Table SIII.2: Age group and gender

Subject were 18 to 55 years of age both inclusive and male.

Table SIII.3: Dose

A single dose [6 mg i.e., 0.6 mL (10 mg/mL)] of either test product BP14 (Pegfilgrastim) 6 mg/0.6 mL solution for Injection or reference product 'Neulasta' (Pegfilgrastim) 6 mg/0.6 mL solution for Injection was administered during the studies to the subjects.

Table SIII.4: Ethnic origin

Ethnicity is summarized below:

Table 4: Ethnicity and race of enrolled subjects in the studies BP14-101 and C1B02880

Characteristics	**Sequence AB@ (N=154) n (%)**	**Sequence BA# (N=154) n (%)**	**Overall (N=308) n (%)**
Ethnicity			
Hispanic or Latino	8 (5.2)	7 (4.5)	15 (4.9)
Not Hispanic or Latino	142 (92.2)	138 (90.0)	280 (91.0)
Not Stated	3 (1.9)	6 (3.9)	9 (2.9)
Unknown	1 (0.6)	3 (1.9)	4 (1.3)
Race			
American Indian or Alaska Native	0	1 (0.6)	1 (0.3)
Asian	102 (66.2)	102 (66.2)	204 (66.2)
Black or African American	1 (0.6)	3 (1.9)	4 (1.3)
Native Hawaiian or Other Pacific Islander	2 (1.3)	1 (0.6)	3 (0.9)
White	47 (30.5)	45 (29.2)	92 (29.8)
Other	2 (1.3)	2 (1.3)	4 (1.3)

@ Sequence AB = Dyrupeg - Neulasta®
# Sequence BA = Neulasta® - Dyrupeg

Part II: Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 5: Exclusion criteria in clinical trials and discussion

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
BP14-101: • Current or previous cancer, diabetes, or any clinically significant cardiovascular, metabolic, renal, hepatic, gastrointestinal, hematologic, respiratory, dermatological, neurological, psychiatric, or any other disorder clinically relevant as judged by the Investigator. • History of chronic cough, fever or acute respiratory illness within 4 weeks prior to the day of IMP administration. • Known or suspected allergic reaction to latex. • Any past or concurrent medical conditions that could have potentially increased the subject's risks or could have affected the evaluation of any study results. The Investigator took a final call on any medical condition that could have interfered in the study results or potentially increased the subject's risk. • Hypersensitivity to the constituents of Neulasta®, pegfilgrastim (sorbitol E420, polysorbate 20 and acetate or acetic acid) or hypersensitivity to E. coli derived proteins. • Any history of major surgery that in the opinion of the Investigator would have interfered with the study or would have placed the subject at risk. • Hereditary fructose and/or sorbitol intolerance. • Any history of previous exposure to pegfilgrastim or filgrastim or known allergy to PEG or any similar analogue.	To assure a homogenous subject population without accompanying diseases interfering with the conduct and scientific evaluation of the results, and to minimize risk to the subjects' welfare.	According to the indications of Pegfilgrastim, the population suitable for treatment in practice will include patients with a clinically significant laboratory abnormality or other clinical findings indicative of a clinically significant disease.

• Treatment with non-topical medications within 5 days prior to first admission to the study center, with the exception of over the counter medications (such as paracetamol, acetaminophen, vitamins, minerals, or health supplements) which in the Investigator's judgment did not interfere with IMP administration or the subject's ability to participate in the study. • Participation in a drug study involving hematopoetic growth factors, monoclonal antibodies, or immunoglobulins in the last 6 months prior to first administration of IMPs or was on a follow-up visit for any other drug studies at the time of screening. • Unable to follow protocol instructions in the opinion of the Investigator. • Donation or loss of more than 500 mL of blood over a period of 90 days prior to first IMP administration • Positive drug screen for alcohol and drugs of abuse (opiates, methadone, methamphetamines, phencyclidine, tetrahydrocannabinol, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants and alcohol) at screening and admission (Day -1), unless a positive result was attributable to a documented use of a concomitant medication and was approved by the Investigator. (In case of positive urine drug screen at screening or on Day -1 of Period 1, at the Investigator's discretion, the drug screen test could be repeated in the possible instance of a false positive due to i.e., poppy seed consumption.) • History of alcohol abuse or excessive intake of alcohol in the past 2 years as judged by the Investigator. • Positive screen on hepatitis B surface antigen (HBsAg), hepatitis B core antibody, anti-hepatitis C virus (HCV) antibodies, or anti-		

human immunodeficiency virus (HIV) 1/2 antibodies at screening. • Family history of acute myeloid leukemia or subjects with splenomegaly (spleen size > 13 cm in the craniocaudal dimension by ultrasound) at baseline, or with sickle cell disease. • Involvement of any Aurobindo Pharma Ltd., Curateq Biologics Pvt Ltd., CRO or study site employee or their close relatives **C1B02880:** • History of allergic responses to Pegfilgrastim, filgrastim, Escherichia coli (E. coli)-derived proteins or other related drugs, or any of its formulation ingredients. History of allergic reactions or hypersensitivity to acetate/acetic acid, polysorbate 20, or sorbitol. • Had significant diseases or clinically significant abnormal findings during screening [medical history, physical examination (clinical examination), laboratory evaluations, ECG, chest X-ray recording and ultrasonography abdomen]. • Any disease or condition like diabetes, psychosis or others, which might compromise the haemopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system or any other body system. • History or presence of bronchial asthma. • Used any hormone replacement therapy within 3 months prior to the first dose of study medication. • Used any depot injection or implant of any drug within 3 months prior to the first dose of study medication. • Used CYP enzyme inhibitors or inducers within 30 days prior to the first dose of study medication (see https://drug-interactions.medicine.iu.edu/MainTable.aspx). • History or evidence of drug dependence or of alcoholism or of moderate alcohol use. • Smokers who smoked 10 or more cigarettes per day or 20 or more biddies per day or those who could not refrain from smoking during the study period.		

• History of difficulty with donating blood or difficulty in accessibility of veins. • A positive hepatitis screen (includes subtypes B and C). • A positive test result for HIV antibody. • Volunteers who had received a known investigational drug within seven elimination half-life of the administered drug prior to the first dose of study medication. • Volunteers who had donated blood or loss of blood 50 ml to 100 ml within 30 days or 101 ml to 200 ml within 60 days or >200 ml within 90 days (excluding volume drawn at screening for this study) prior to first dose of study medication, whichever was greater. • Intolerance to venipuncture. • Any food allergy, intolerance, restriction or special diet that, in the opinion of the principal investigator or sub-investigator, could contraindicate the volunteer's participation in this study. • Institutionalized volunteers. • Used any prescribed medications within 14 days prior to the first dose of study medication. • Used any OTC products, vitamin and herbal products, etc., within 7 days prior to the first dose of study medication. • Used grapefruit and grapefruit containing products within 7 days prior to the first dose of study medication. • Ingestion of any caffeine or xanthine products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.), cigarettes and tobacco containing products, recreational drugs, alcohol or other alcohol containing products within 48 hours prior to the first dose of study medication. • Ingestion of any unusual diet, for whatever reason (e.g.: low sodium) for three weeks prior to the first dose of study medication. • Volunteer had Total WBC count higher than the upper limit of normal range during screening. • Volunteer had Platelets counts lower than the lower limit of normal range during screening.		

• Volunteer had Serum creatinine and serum bilirubin higher than the upper limit of normal range during screening. • Volunteer had SGPT, SGOT and Alkaline phosphatase higher than 1.1 times of upper limit of normal range during screening. • Volunteers who had any past exposure to recombinant human G-CSF products and/or a known history of prior treatment with blood-cell colony stimulating factors, interleukins or interferons. • Volunteer with history of cancer. • Volunteers who were on a special diet or who have self-reported a weight loss of more than 15 pounds (6.8 kg) within 1 month prior to initial dosing. • Acute viral or bacterial infection within 1 month prior to initial dosing only if considered clinically significant in the opinion of the principal or sub-investigator. • History of any clinically significant disease or condition that, in the opinion of the principal or sub-investigator or physician, would render them unsuitable for inclusion in the study.		

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table: 6: **Exposure of special populations included or not in clinical trial development programmes**

Type of special population	Exposure
Pregnant women	There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity. Pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

	There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known.
Breastfeeding women	There is insufficient information on the excretion of pegfilgrastim/metabolites in human breast milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from pegfilgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Patients with relevant comorbidities: • Patients with hepatic impairment	Uncommon elevations in liver function tests (LFTs) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline
• Patients with renal impairment	Granulocytecolony stimulating factor, is eliminated by kidney during chemotherapy-induced neutropenia and therefore must be given daily to maintain the desired therapeutic effects.
• Patients with cardiovascular impairment	Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers

• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Pharmacogenomics or genetics are not evaluated in this study
Other	Not applicable

Part II: Module SV Post-authorisation experience

Not applicable

Part II: Module SVI –additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Due to the drug class and mode of action, abuse is not expected.

Part II: Module SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Capillary leak syndrome

Risk-benefit impact:

Capillary leak syndrome, although rare, is a serious adverse reaction that can be potentially life threatening and has been reported after G-CSF administration.

Important Identified Risk: Acute respiratory distress syndrome

Risk-benefit impact:

Acute respiratory distress syndrome is a life-threatening adverse reaction. The adverse reaction was identified through post-marketing surveillance, but was not observed in randomised clinical trials on adults.

Important Identified Risk: Sickle cell crisis in patients with sickle cell disease

Risk-benefit impact:

Sickle cell disease can vary from mild to serious. Severe and possibly fatal sickle cell crises can occur in patients with sickle cell disorders receiving G-CSF.

Important Identified Risk: Glomerulonephritis

Risk-benefit impact:

Glomerulonephritis, a serious adverse reaction, that can potentially be life-threatening, has been reported in patients receiving filgrastim and pegfilgrastim.

Important Potential: Risk: Cytokine release syndrome

Risk-benefit impact:

Cytokine release can present with a variety of symptoms ranging from mild, flu-like symptoms and some patients may experience severe, life-threatening reactions requiring urgent medical attention. Cytokine release syndrome is included as a potential risk after consideration of the available evidence and PRAC review of cases retrieved from EudraVigilance and scientific literature.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing Information

SVII.3.1. Presentation of important identified risks and important potential risks

Table 7: Important identified risk

Identified Risk	Capillary leak syndrome
Potential mechanisms	CLS has been reported in patients with cancer undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor-cell mobilisation who were receiving filgrastim or pegfilgrastim. Reports have generally involved people with advanced malignant disease, sepsis, those taking multiple chemotherapy medicines, or those undergoing apheresis. The mechanism of CLS remains unclear.
Evidence Source (s) and strength of evidence:	In accordance with the in line with innovator (Neulasta)

Characterisation of the risk:	There are less than 500 patients with SCLS reported in the world literature since its first description in 1960 by Clarkson. Although most clinical studies were performed in Caucasians, SCLS has been recognized in a range of racial backgrounds and nationalities. SCLS seems to occur slightly more often in older male adults, but females have also been affected. Most diagnoses are made at the median age of 48 years of age. The disease may be more frequent than the literature suggests because the diagnosis is often missed or delayed[2].
Risk groups or Risk factors	Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins (Kai-Feng et al, BMC Cancer, 2011;11:204), gemcitabine (Baron et al, Clin Oncol (R Coll Radiol), 2006;18:90-91), doxorubicin (Krzesiński et al, Cardiol J, 2010;17:88-91), granulocyte-macrophage colony-stimulating (Al-Homaidhi et al, Bone Marrow Transpl, 1998;21(2):209-214), and interferon (Yamamoto et al, Arch Intern Med, 2002;25:481-482). Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis (Kai-Feng et al, BMC Cancer, 2011; 11:204).
Preventability	Physicians and oncologists should be aware of secondary CLS in cancer patients during anti-cancer treatment, and encourage careful observation to prevent CLS or enable timely management when CLS develops. Patients should tell the doctor immediately if they have any of the following or combination of the following side effects: Swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion
Impact on the risk-benefit balance of the product	No change to risk minimization is warranted at this time. This risk can be minimised through the product information
Public health impact	Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of G-CSFs

Table 8: Important identified risk

Identified Risk	**Acute respiratory distress syndrome**
Potential mechanism	Administration of granulocyte and macrophage colony-stimulating factors, while useful, should be treated with caution as the upregulation of cytokines that increase alveolar permeability or neutrophil influx (such as TNF-α, IL-1β and IL-8) can exacerbate acute lung injury. Activated neutrophils have been implicated in the development of ARDS via effects on microvascular injury and vascular permeability. Furthermore, increasing concentration of endogenous G-CSF has been associated with the severity of lung injury in ARDS and acute lung injury, both in bronchioalveolar lavage fluid (BALF) and serum, in addition to elevations in BALF IL-8

Evidence Source(s) and strength of evidence:	In accordance with the in line with innovator (Neulasta)
Characterisation of the risk:	Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of acute respiratory distress syndrome (ARDS).
Risk groups or risk factors	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in non-Hodgkin's lymphoma (NHL) (Huang et al, Ann Hematol, 2011; 90:1145-1151; Katsuya et al, Leukaemia & lymphoma, 2009; 50:1818-1823). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, J Clin Onc, 1984;2:396-405), particularly in Japan (Camus et al, Br J Cancer, 2004;91 Suppl 2:S18-23).
Preventability	Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving pegfilgratism, for ARDS. Patients should see their doctor if they have symptoms such as cough fever, and shortness of breath that could be preliminary signs of ARDS
Impact on the risk-benefit balance of the product	No change to risk minimization is warranted at this time. This risk can be minimised through the product information
Public Health Impact	Increased pegfilgrastim exposure leading to greater risk of treatment-related AEs.

Table 9: Important identified risk

Identified Risk	**Sickle cell crisis in patients with sickle cell disease**
Potential mechanisms	There is a dearth of literature regarding the use of G-CSF and its related pegylated forms in patients with sickle cell anemia and sickle cell trait. Mechanisms postulated include the sudden elevation in granulocytes, neutrophil activation, and cytokine release along with possible increased leukocyte adhesion leading to a cascade of events causing vaso-occlusion in patients with sickle cell anemia
Evidence Source(s) and strength of evidence:	In accordance with the in line with innovator (Neulasta)
Characterisation of the risk:	The heterozygous form of sickle cell anaemia, sickle cell trait (SCT), is present in up to 8% of African-Americans in the United States. Higher prevalence of up to 25% has been reported in some populations, but it is very rare to find sickle cell disease or trait in Caucasians. Although

	considered a benign disorder, it has been associated with numerous complications and adverse events, more so when exposed to conditions that would promote sickling, for example, periods of stress or high altitude[3].
Risk groups or risk factors	Patients with sickle cell disease are at risk for sickle cell crisis (Rees et al, Lancet, 2010; 376:2018-2031). Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (e.g, sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis(Yale et al, Am Fam Physician, 2000;61:1349-1356,1363-1344).
Preventability	Sev Patients with sickle cell disease should receive pegfilgrastim only after careful evaluation of both risks and benefits of treatment.
Impact on the risk-benefit balance of the product	No change to risk minimization is warranted at this time. This risk can be minimised through the product information.
Public health impact	Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients)

Table 10: Important identified risk

Identified Risk	**Glomerulonephritis**
Potential mechanisms	Following G-CSF treatment, Myeloperoxidase antibodies were formed leading to signs and symptoms of Antineutrophilic cytoplasmic antibody (ANCA) vasculitis correlating to a Birmingham vasculitis activity score (BVAS) of 18 'new' points. The activated neutrophils were attracted to the formerly deposited immunoglobulins and complement in the glomeruli, leading to the formation of a cellular (indicating fresh) crescent as well as fresh thrombi thus serving as a 'second hit'. This cascade of events could have easily gone unnoticed if no baseline glomerulopathy had been present
Evidence Source(s) and strength of evidence:	In accordance with the in line with innovator (Neulasta)
Characterisation of the risk:	Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of pefilgrastim and filgrastim.
Risk groups or risk factors	Other than the cancer itself, no specific risk factors were identified for this patient population.
Preventability	Glomerulonephritis has occurred in patients receiving pegfilgrastim. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of pefilgrastim.
Impact on the risk-benefit balance of the product	No change to risk minimization is warranted at this time. This risk can be minimised through the product information.

Public health impact	Glomerulonephritis has been reported as uncommon (≥ 1/1,000 to < 1/100) and it may lead to increased and prolonged hospitalisations, either from elevated pregfilgastim exposure.

Table 11: Important potential risk

Potential Risk	**Cytokine release syndrome**
Potential mechanisms	G-CSF acts by stimulating myeloid progenitor cells and potentially exacerbating the severity of Cytokine release syndrome
Evidence Source(s) and strength of evidence:	In accordance with the in line with innovator (Neulasta)
Characterisation of the risk:	Patient characteristics were similar for the two cohorts (below table). Over 92% of the patients were evaluable for their history of prior lines of treatment, and there were no significant differences with respect to predictors for poor mobilization such as prior exposure to alkylating agents, radiation to the marrow-bearing bone, prior fludarabine exposure (which has previously been associated with poor mobilization)34, 35, 36 or rate of plasma cell disorders in the filgrastim group; a factor that can be associated with better stem cell collections[4]

	Filgrastim	***Pegfilgrastim***	**P**
n	30	22	
Age median(range)	56 (42–78)	50 (40–69)	0.111
Male:Female *N*	19:11	12:10	0.576
Body weight (kg) median (range)	79.5 (57–103)	81 (51–126)	0.850
Disease %(95% CI), (N)			
NHL—indolent	40% (23–59%) (12)	45% (24–68%) (10)	0.400
NHL—aggressive	10% (2–27%) (3)	14% (3–35%) (3)	1.000
Plasma cell disorders	40% (23–59%) (12)	23% (8–45%) (5)	0.240
Hodgkin lymphoma	3% (0–17%) (1)	14% (3–35%) (3)	0.300

	Other	7% (1–22%) (2)	3% (0–23%) (1)	1.000
	Lines of prior therapy mean (range) [a]	1 (0–6)	1 (0–2)	0.130
	Prior alkylator exposure % (*N*)	15% (4–34%) (4/27)	14% (3–36%) (3/21)	
	Prior fludarabine exposure % (*N*)	4% (0–19%) (1/27)	10% (1–30%) (2/21)	
	Prior radiotherapy to red marrow % (*N*)	7% (1–24%) (2/27)	5% (0–24%) (1/21)	
	Prior mobilization attempt %(95% CI), (N)	30% (15–49%) (9)	9% (1–29%) (2)	1.000
	Prior failed mobilization attempt %(95% CI), (N)	13% (4–31%) (4)	9% (1–29%) (2)	1.000
	Current mobilization regimen % (*N*):			
	Filgrastim 10 mcg/kg/d from D1	100% (30)		
	Pegfilgrastim 6mg stat D1		10% (2)	
	Pegfilgrastim 12 mg stat D1		90% (20	
Risk groups or Risk factors	Patients receiving bi-specific antibodies and T cells engineered to express anti-CD19 chimeric antigen receptor are at particularly high risk for cytokine release syndrome (Frey, Best Pract Res Clin Haematol, 2017;30(4):336-340). The severity of the cytokine release syndrome mediating infusion reaction might be related to the number of circulating lymphocytes (Chung, Oncologist, 2008; 13:725-732). Among patients with B-cell malignancies, risk factors for developing cytokine release syndrome included higher bone marrow tumor burden, higher chimeric antigen receptor T-cell (CAR-T) cell dose, bulk CD8+ T-cell selection, lymphodepletion using fludarabine/ cyclophosphamide, and presence of thrombocytopeniabefore lymphodepletion (Hay et al, Blood, 2017;130(21):2295-2306).			
	None			

Preventability	
Impact on the risk-benefit balance of the product	No change to risk minimization is warranted at this time. This risk can be minimised through the product information.
public health impact	Increased Pegfilgrastim exposure leading to greater risk of treatment-related AEs.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table 12: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Capillary leak syndrome
	Acute respiratory distress syndrome
	Sickle cell crisis in patients with sickle cell disease
	Glomerulonephritis
Important potential risks	Cytokine release syndrome
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Maintaining the Global Pharmacovigilance System according to EU/UK regulations and the Company's procedures. Also collection, processing, assessment and reporting of Individual case safety report (ICSR), routine literature screening of EU/UK journals for ICSRs and worldwide indexed journals, production of a Periodic Safety Update Report (PSUR) for all products that the MAH markets in EU/UK and Signal detection to monitor, detect and evaluate any new safety concerns and Other requirements, as defined by local regulations.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse event follow-up questionnaires for events "Capillary leak syndrome" and "Cytokine release syndrome" have been developed to obtain all relevant information for each individual case safety report for these events from the reporter.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are recommended**.**

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Table 13: Important Identified Risk

Safety concern	Routine risk minimisation activities
Capillary leak syndrome	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: Symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care Prescription only medicine.

Safety concern	Routine risk minimisation activities
Sickle cells crisis in patients with sickle cell disease	Routine risk communication: Listings in SmPC section 4.4. Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim Other routine risk minimisation measures beyond the Product Information: Physicians should use caution when prescribing pegfilgrastim in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

	○ Prescription only medicine.

Safety concern	Routine risk minimisation activities
Glomerulonephritis	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: Urinalysis monitoring is recommended. ○ Prescription only medicine.

Safety concern	Routine risk minimisation activities
Acute respiratory distress syndrome	Routine risk communication: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: Prescription only medicine.

Important Potential Risk:

Safety concern	Routine risk minimisation activities

Cytokine release syndrome	Routine risk communication: None proposed Other routine risk minimisation measures beyond the Product Information: o Prescription only medicine.

Missing information:

None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table 14: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Capillary leak syndrome	Routine risk minimisation measures: Listings in SmPC section 4.4 Special warnings andprecautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: Symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care o Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Sickle cells crisis in patients with sickle cell disease	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

	Listings in SmPC section 4.4. Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim Other routine risk minimisation measures beyond the Product Information: Physicians should use caution when prescribing pegfilgrastim in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis. o Prescription only medicine.	reactions reporting and signal detection: None
Glomerulonephritis	Routine risk minimisation measures: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: Urinalysis monitoring is recommended. o Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Acute respiratory distress syndrome	Routine risk minimisation measures: Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects Other routine risk minimisation measures beyond the Product Information: o Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Important Potential Risks		

Cytokine release syndrome	Routine risk minimisation measures: None proposed Other routine risk minimisation measures beyond the Product Information: Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Missing information None		

Part VI: Summary of the risk management plan

Summary of risk management plan for Dyrupeg 6mg/0.6mL solution for injection in pre-filled syringe (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Dyrupeg 6mg/0.6mL solution for injection in pre-filled syringe (hereinafter referred to as Dyrupeg). The RMP details important risks of Dyrupeg, how these risks can be minimised, and how more information will be obtained about Dyrupeg's risks and uncertainties (missing information).

Dyrupeg's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dyrupeg should be used.

This summary of the RMP for Dyrupeg should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dyrupeg's RMP.

I. The medicine and what it is used for

Dyrupeg is authorised for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and Myelodysplastic syndromes). (See SmPC for full indications). It contains Pegfilgrastism as the active substance and is given subcutaneously.

Further information about the evaluation of Dyrupeg's benefits can be found in Dyrupeg's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Dyrupeg, together with measures to minimise such risks and the proposed studies for learning more about Dyrupeg's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about the adverse reactions is collected continuously and regularly analysed including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Dyrupeg are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by the patient. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dyrupeg. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important Identified risks	Capillary leak syndrome
	Sickle cells crisis in patients with sickle cell disease
	Glomerulonephritis
	Acute respiratory distress syndrome
Important potential risks	Cytokine release syndrome
Missing information	None

II.B Summary of important risks

Important identified risk	
Capillary leak syndrome	
Evidence for linking the risk to the medicine	In accordance with the in line with innovator (Neulasta)
Risk factors and risk groups	Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins, gemcitabine doxorubicin, granulocyte-macrophage colony-stimulating, and interferon. Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis.
Risk minimisation measures	Routine risk minimisation measures: • Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects • Listings in PIL section 2. What you need to know before youuse pegfilgrastim and 4. Possible side effects • Prescription only medicine Additional Risk Minimisation Measures: • None

Important identified risk	
Sickle cells crisis in patients with sickle cell disease	
Evidence for linking the risk to the medicine	In accordance with the in line with innovator (Neulasta)
Risk factors and risk groups	Patients with sickle cell disease are at risk for sickle cell crisis. Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (eg, sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis.

Risk minimisation measures	Routine risk minimisation measures: • Listings in SmPC section 4.4. Special warnings and precautions for use and 4.8 Undesirable effects • Listings in PIL section 2. What you need to know before you use pegfilgrastim • Prescription only medicine Additional Risk Minimisation Measures: • None

Important identified risk	
Glomerulonephritis	
Evidence for linking the risk to the medicine	In accordance with the in line with innovator (Neulasta)
Risk factors and risk groups	Other than the cancer itself, no specific risk factors were identified for this patient population.
Risk minimisation measures	Routine risk minimisation measures: • Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects • Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects • Prescription only medicine Additional Risk Minimisation Measures: • None

Important identified risk	
Acute respiratory distress syndrome	
Evidence for linking the risk to the medicine	In accordance with the in line with innovator (Neulasta)
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in non-Hodgkin's lymphoma (NHL). Interstitial pneumonitis and other interstitial lung

	diseases have been seen with other chemotherapy agents in the setting of lungcancer, particularly in Japan.
Risk minimisation measures	Routine risk minimisation measures: • Listings in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects • Listings in PIL section 2. What you need to know before you use pegfilgrastim and 4. Possible side effects • Prescription only medicine Additional Risk Minimisation Measures: • None

Important potential risk	
Cytokine release syndrome	
Evidence for linking the risk to the medicine	In accordance with the in line with innovator (Neulasta)
Risk factors and risk groups	Patients receiving bi-specific antibodies and T cells engineered to express anti-CD19 chimeric antigen receptor are at particularly high risk for cytokine release syndrome. The severity of the cytokine release syndrome mediating infusion reaction might be related to the number of circulating lymphocytes. Among patients with B-cell malignancies, risk factors for developing cytokine release syndrome included higher bone marrow tumor burden, higher chimeric antigen receptor T-cell (CAR-T) cell dose, bulk CD8+ T-cell selection, lymphodepletion using fludarabine/ cyclophosphamide, and presence of thrombocytopenia before lymphodepletion.
Risk minimisation measures	Routine risk minimisation measures: • Prescription only medicine. Additional Risk Minimisation Measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Dyrupeg.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Dyrupeg

Part VII: Annexes

Table of contents

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not Applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 – Specific adverse drug reaction follow-up forms

Annex 4.1 Specific adverse event follow-up questionnaire “Capillary leak syndrome”

Annex 4.2 Specific adverse event follow-up questionnaire “Cytokine release syndrome”

Specific adverse event follow-up questionnaires are enclosed overleaf.

Annex 5 –Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

1. CHMP, *Neulasta EPAR-Scientific Discussion,* EMA. 2009
2. Rare Disease Database*, Systemic Capillary Leak Syndrome*, NORD
3. Safety of Pegfilgrastim (Neulasta) in Patients with Sickle Cell Trait/Anemia; Mrinal M. Patnaik,2 and Prema P. Peethambaram2; Volume 2013 |Article ID 146938 | ttps://doi.org/10.1155/2013/146938
4. Pegfilgrastim compared with filgrastim for cytokine-alone mobilization of autologous haematopoietic stem and progenitor cells; K E Herbert, P Gambell, E K Link, et. al; www.nature.com/articles/bmt201214

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval Date Procedure	Change
0.1	N/A Centralised (H0006407)	Initial submission
0.2	N/A Centralised (H0006407)	Version 0.1 RMP has been updated as per the assessor comments. Part II: Module SIII has been updated to include pooled data for the conducted studies, and to remove the specific data on subjects who prematurely withdrew from the clinical studies. Part II: Module SVII, SVII.1.1 has been updated to be in line with the reference medicinal product, and the risk of medication errors was removed. Annex 4 has been updated with the Specific adverse event follow-up questionnaires for Capillary leak syndrome, and Cytokine release syndrome.
0.3	N/A Centralised (H0006407)	Version 0.2 RMP has been updated as per the comment received from EMA. Part VI "Summary of the Risk Management Plan" has been updated to be in line with the issue raised in other parts of RMP, as per D180.